Kidney International, Vol. 57, Suppl. 74 (2000), pp. S-3–S-6

METHODOLOGIC APPROACH

Role of observational studies versus clinical trials in ESRD research

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Role of observational studies versus clinical trials in ESRD research. Randomized controlled clinical trials have been considered by many to be the only reliable source for information in health services research. This review considers the advantages and limitations of observational studies as compared to randomized clinical trials. It presents specific examples of scientific research done with observational registry data to show that some research is more feasible with an observational approach and that this approach may lead to better designs of prospective clinical trials. Such trials continue to be the gold standard in outcomes research.

Much of the research in ESRD has been based on observational studies, and a large portion of the scientific knowledge in this field comes from registry studies. Numerous national and regional registries of patients treated for ESRD are currently in existence [1]. The purpose of this review is to assess the advantages and limitations of observational studies compared to randomized, controlled, clinical trials in research that focuses on outcomes. The following review and discussion will focus particularly on observational studies that are population-based, such as studies of registries, although much of the discussion is also relevant for larger single- or multicenter studies. Examples will largely be drawn from USRDS studies.

PATIENT AND TREATMENT ASSIGNMENT

One of the most basic differences between observational studies and randomized controlled clinical trials lies in the design and assignment of patients and treatments. In the randomized, controlled trial, the treatment assignment is random, i.e., patients are assigned randomly to one treatment or another. An advantage of the random assignment is the control of confounding factors both known and unknown. The assignment of patients, however, usually is not representative of all patients, since it is nonrandom due to selection and exclusion criteria. For example, patients may be excluded for lack of consent or for noncompliance. An example of this problem can be found in the Modification of Diet and Renal Disease Study (MDRD), where the randomization to a low protein and a very low protein diet excluded a large fraction of patients because of the difficulties in following severe dietary restrictions [2]. Therefore, this study can be extrapolated only to those patients who would be able and willing to follow such a strict diet, while it may not be applicable to other patients. This and similar studies observe the *efficacy* of a treatment, i.e., what the treatment A vs. treatment B can accomplish (perhaps under ideal circumstances).

In contrast, many population-based observational studies select patients at random and the treatment assignment is nonrandom. Such studies may thus be representative of all patients. If, for example, children were excluded, then the results would still be representative, but only of adult patients. The emphasis of such studies is to evaluate the *efficiency* of treatment A vs. treatment B as delivered under real world conditions, which may be less than ideal and include patients who are not compliant. The findings of such a study are more easily extrapolated to the population at large (while considering applicable exclusion criteria). Control for confounding factors is limited to those factors that are recognized and measured, while adjustment for unknown factors is not possible.

TIME TO COMPLETION OF STUDY

Truly prospective observational studies and randomized controlled trials may require a similar time frame to completion. However, observational studies of historical cohorts can be completed within a substantially shorter time frame. This retrospective approach may allow the study to begin at a time in the past, and all follow-up of interest may already be available at the time of data abstraction. This design may be labeled "historically pro-

spective" if the data collection follows strict rules for abstracting baseline data while not allowing any data after the baseline date to enter consideration, except, of course, the outcome(s) of interest. The ascertainment of coronary artery disease at study start may serve as an example: A patient with no evidence in the medical records at study start may, a week later, be admitted with an acute myocardial infarction. Even though this new evidence indicates that coronary artery disease must have been present at study start, the prospective approach requires coding of coronary disease as being absent at study start because evidence was lacking at that time. Thus, a historical prospective study is designed like a prospective study with a fixed study start date, located in the past, using only data that would have been available at or before that date. This approach saves the time of waiting for the outcome events to accumulate during the follow-up period, as the follow-up period of interest is already available. However, a critical ingredient is that the availability of data (e.g., of medical records) must not vary according to the study outcome. This historical prospective approach has been successfully utilized by many studies of the United States Renal Data System (USRDS) [3–5].

NUMBER OF HYPOTHESES

Clinical trials frequently test only one or two main hypotheses, sometimes with some secondary goals. Observational studies may be designed to test numerous hypotheses. The Hemodialysis (HEMO) Trial may serve as an example of the former with two hypotheses that dialysis dose and dialysis membranes are each independently associated with outcomes [6]. Testing a third hypothesis would have required eight study groups instead of four for this trial.

The USRDS Case Mix Adequacy Study may serve as an example of many hypotheses tested in a single sampling frame and data collection instrument. When adjusting for patient demographics, comorbid conditions, and selected laboratory values, this study evaluated mortality risk as the primary outcome by dialysis dose, type of membrane, nutrition, control of phosphorus and other factors. The main findings included a strong correlation of lower dialysis dose with higher mortality risk [7], a correlation of dialyzer membrane with mortality even at the same dialysis dose [8], a correlation of nutritional status with mortality risk even after a several year lag period [9], a correlation of hyperphosphatemia with mortality risk [10] with and without adjustment for nutrition, and dialysis dose [11], as well as compliance (Leggat) and a correlation of low middle molecule clearance (measured by vitamin B_{12}) with high mortality risk, even at the same Kt/V for urea [12]. Additional studies [6–8] looked at cause-specific death rates to ascertain which causes of death could be identified as being responsible for the overall correlations with Kt/V [13], membrane [14] and hyperphosphatemia [15]. Thus, a single observational study on a random sample of about 5000 hemodialysis patients led to important new knowledge with respect to several hypotheses. Even lacking results from a prospective trial, these results have had an impact on dialysis practice and likely on patient survival in the United States [16].

COST

Prospective randomized clinical trials tend to be very costly. The recent MDRD and HEMO trials are examples of high cost trials. It appears that cost may be a reason why major trials in ESRD are launched infrequently. Observational studies of existing registries are of comparatively low cost. In the USRDS, data collections on random samples of patients have occured almost on a yearly basis, and each such data collection has tested several hypotheses. Observational study results also may be cost effective by helping to focus questions for randomized trials and estimating the size of the expected effect. The latter is required for the calculation of the needed sample size. For example, the HEMO trial is evaluating the effect of two levels of dialysis dose [6], both being at a level above which the USRDS studies could not determine whether the dialysis dose was still correlated with mortality [7, 17].

Because of the large costs of prospective randomized trials in dialysis, the sample size for most such studies was barely adequate. The National Cooperative Dialysis Study (NCDS) may serve to make that point; most who examined the study data concluded that shorter treatment time was not associated with worse outcomes in a statistically significant fashion ($P > 0.05$) [18]. However, this correlation in fact had a P value of 0.06, suggesting that a slightly larger sample size might have led to a significant conclusion, namely that longer hemodialysis treatment times were associated with better outcomes.

This last major dialysis trial in the U.S. was performed about 20 years ago. The next major clinical trial in U.S. dialysis patients is the current HEMO trial. The MDRD trial on pre-ESRD patients had a cost that exceeded the entire USRDS budget with all its studies, numerous reports and scientific publications in the last 11 years. Therefore, it appears from my vantage point (perhaps biased) that observational studies complement major trials and often yield clinically useful information at a substantially lower cost.

CAUSATION AND CORRELATION

Double-blind, randomized trials allow inference of causality if the trial is well designed, the result is positive,

and power is sufficient, i.e., there is a statistically significant result. Observational studies like those of the USRDS only report associations; however, they have affected clinical practice in the U.S. and perhaps elsewhere. One may argue that observational study results of USRDS and others have been responsible for the marked improvement in the survival of dialysis patients [16]. Reasons for acceptance of observational study results in clinical practice include the magnitude of the observation and the pathophysiologic plausibility. Additionally, the stability of the finding ("robustness") when modifying statistical adjustments to consider confounders in sensitivity analyses provides a stronger suggestion of causality. Since observational studies often cannot come to firm conclusions regarding the causality, they are sometimes called "hypothesis-generating." Thus, it is not unusual for observational studies to help focus and design subsequent clinical trial.

FEASIBILITY

Many study questions cannot be addressed by randomized clinical trial because denying patients appropriate treatment in the name of research is not ethical. For example, it may not be feasible and justifiable to randomize patients into two ESRD treatment options such as dialysis vs. transplantation. In an observational study, we have shown that the mortality risk is high during the first weeks after transplantation, then equal and later markedly better for a cumulative gain, compared to an appropriate control group of dialysis patients on the transplant waiting list. This was done without randomization and not dependent on the practice at a particular center, and describes the actual practice across a population [19, 20]. Such a study would not be feasible as a randomized trial. Similarly, ethical reasons restricted the HEMO trial to randomize patients only to an average or acceptable Kt/V vs. a high Kt/V. It was not appropriate to randomize patients to a treatment level below the average dialysis dose. By contrast, the observational studies of outcomes by dialysis dose had no such restriction and included patients over the entire spectrum of Kt/V, including those who received a below average Kt/V [7, 21]. Controlled clinical trials have been few in number in ESRD, and many have focused on specific drugs rather than renal replacement therapy itself.

CONCLUSION

There is no question that randomized, controlled clinical trials are the gold standard in outcome research. Their main limitations of testing only few hypotheses at a relatively high cost are overcome by observational studies. The latter, however, have the chief limitation of showing correlations without directly proving causation. Observational studies can be performed in areas where prospective trials have ethical restrictions. Both clinical trials and observational studies therefore have specific roles. They may complement one another, as when the observational study leads to a hypothesis, which can be answered in a well-designed clinical trial. Furthermore, data from an observational study may help develop a new trial by suggesting sample size requirements and optimal design.

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